UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JORDAN J. N. TANG and ARUN K. GHOSH

Appeal No. 2005-0106
Application No. 09/506,988

ON BRIEF

Before ELLIS, ADAMS and GRIMES, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 4, 6-8, 10 and 12. The examiner has indicated that claims 5 and 11 would be allowable if written in an independent form. Answer, p. 9. Claims 3 and 9 have been canceled.

Claims 1, 2, 4 and 7 are representative of the subject matter on appeal and read as follows:

> 1. A polypeptide aspartic acid protease inhibitor comprising two or more transition-state isosteres in the polypeptide backbone, which have different orientations that mimic the transition state of the aspartic acid protease, and bind to different subsite binding pockets in the aspartic acid protease.
>
> 2. The inhibitor of claim 1 wherein the transition-state isotere is $-CH(OH)-CH_2-$.
>
> 4. The composition of claim 1 wherein the aspartic acid protease inhibitor is an HIV protease inhibitor.
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> 7. A method for treating a patient infected with a pathogen expressing an aspartic acid protease comprising the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

The references relied upon by the examiner are:

Jadhav (Jadhav I)	5,491,149	Feb. 13, 1996
Jadhav et al. (Jadhav II)	5,683,999	Nov. 4, 1997

Vacca, Joseph P., "Design of Tight-Binding Human Immunodeficiency Virus Type I Protease Inhibitors," Methods in Enzymology, Vol. 241, pp. 311-334 (1994).

The claims stand rejected as follows:

I. Claims 1, 2, 4, 6-8, 10 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

II. Claims 1, 2, 4, 6-8, 10 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, had possession of the claimed invention at the time the application was filed.

III. Claims 1, 2, 4, 6-8, 10 and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Jadhav I and Jadhav II.

We have carefully considered the respective positions of both the examiner and the appellants. We agree with the appellants with respect to Rejections I and II and, therefore, reverse those two rejections. However, we affirm Rejection III.

Background

As indicated by the claims above, the present invention is directed to modified aspartic acid protease inhibitors having two or more transition-state isosteres and methods of treating a patient infected with a pathogen, including HIV, using said inhibitors.

According to the specification, drug resistance is a problem in treating most pathogenic infections. Specification, p. 1. With respect to HIV, in particular, it is said that this problem is minimized by using a mixture of two or three different drugs to block the life cycle before the virus can develop drug resistance. Id. Currently, the most widespread treatment of HIV is said to involve the use of one or two nucleoside drugs

that inhibit replication by intercalating into the viral nucleic acid, in combination with a protease inhibitor. Id.

The HIV protease is an enzyme which processes the gag and pol polypeptides of the virus into structural proteins and enzymes needed for the assembly of infectious virions. Id. Mutations of the active site of the retroviral protease are said to render the virus non-infective; thus, it has become a target for viral therapy. Id.; see also, Vacca, "Design of Tight-Binding Human Immunodeficiency Virus Type I Protease Inhibitors," in Methods in Enzymology, vol. 241, pp. 311-334 (1994), p. 311.

The specification discloses that the active site of the HIV protease is located between two monomers which each contribute an aspartic acid residue to form the catalytic site. Specification, p. 2, last para.; Vacca, p. 311, first complete para. Thus, the HIV protease is a member of the family of aspartic acid proteases. According to the specification, the first transition-state analogue of aspartic proteases discovered was the isostere CH(OH)-CH_2- which was found by prior investigators "to mimic the transition state of catalysis with two carbons in tetrahedral conformation, as [sic, in?] contrast to the planar conformation of the peptide bond in the substrate." Id., p. 3, lines 23-27. The specification discloses that each of the four commercial HIVPr [HIV protease] inhibitors currently available contains an isostere CH(OH)-CH_2- which mimics the transition state (tetrahedral intermediate) which occurs during the hydrolysis of the peptide bond. Id., p. 3, lines 6-27; Vacca, p. 312. Other types of isosteres shown to be

effective as aspartic proteases are said to include "hydroxyethylene, dihydroxyethylene [-CH(OH)-CH(OH)-], hydroxyethylamine [-CH(OH)-CH_2-NH-], phosphinate [-PO(OH)-CH_2-] and reduced amide [-CH_2-NH-]." Specification, p. 4, lines 3-5.

The protease inhibitors of the present invention are said to differ from the prior art compounds in that they contain two or more -CH(OH)-CH_2- moieties which mimic the transition state in the catalytic mechanism of the protease.

Discussion

I. 35 U.S.C. § 112, first paragraph (enablement)

The examiner argues that it would require undue experimentation to make and use the subject matter set forth in claims 1, 2, 4, 6-8, 10 and 12. Answer, pp. 4-6. The examiner further argues that (i) the claims encompass all compounds having two or more isosteres that mimic the transition state of aspartic acid protease; (ii) the invention is directed to the treatment of any patient infected with a pathogen expressing an aspartic acid protease; (iii) the prior art discloses several compounds that have a single state isostere; (iv) "the level of unpredictability is hard to describe"; and (v) the specification provides "little direction due to the ambiguousness of the definition of transition state isostere"; (vi) the specification discloses four examples of isosteres which are effective as aspartic acid protease inhibitors, but no further direction is provided as to other active compounds; and (vii) the specification provides only one

working example of the claimed invention. Id., pp. 5-6. The examiner concludes that given the lack of direction provided by the specification, it would require undue experimentation for one skilled in the art to make and use the claimed invention. Id., p. 6.

In response, the appellants argue that aspartic acid proteases share a common active site. Brief, p. 10. The appellants further argue that aspartyl protease inhibitors have similar structural and physical properties because of their stereospecificity for a class of proteases with similar active sites. Id. The appellants still further argue that the prior art provides numerous examples of single transition-state isosteres (Figure 1 and Table II at page 18), and that the specification discloses how to make two isostere inhibitors and how to test them. Id., pp. 9-10. Moreover, even if the active site of a particular aspartyl protease is not known in the art, the appellants contend that the core structure can readily be determined using commercially available computer programs. Id. According to the appellants, one skilled in the art can design and construct an inhibitor comprising two or more isosteres without undue experimentation. Id. Thus, the appellants contend that one skilled in the art of organic synthesis can make and use the claimed invention without undue experimentation. Id; Reply Brief, pp. 5-6. The appellants rely on Vacca for support.

It is well established that the specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation.

Enzo Biochem Inc. v. Calgene Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir. 1999); Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); PPG Ind., Inc. v. Guardian Ind. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 495-96, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). "That some experimentation may be required is not fatal, the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444. In determining whether a disclosure would require undue experimentation, the court set forth several factors to be considered. These factors include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Here, the examiner has tried to apply the Wands factors to her analysis of the claimed invention; however, not all of the reasons provided support a prima facie case of non-enablement. See, for example, the examiner's statement with respect to the prior art disclosure of numerous compounds that have a single transition-state isostere (subsection (iii), above), and the lack of direction being due to the ambiguousness of the phrase "transition-state isostere" (subsection (v)). Although not supportive of her position, the statement of these points is not fatal to the rejection since a proper

enablement analysis involves a weighing of the Wands factors. However, we disagree with the examiner's analysis.

We find that in weighing all the factors before us, that the state of the prior art (set forth by the examiner as subsection (iii), above), tips the scale in the appellants' favor. In particular, attention is directed to the Vacca publication which discloses that many transition-state isosteres and their use in the preparation of protease inhibitors were known in the art. Vacca, p. 311. Vacca discloses (p. 311), inter alia, that

> . . . Most potent inhibitors of HIV-1 protease reported are peptidomimetics and are based on the transition-state mimic concept. . . . [E]xamples that outline the approach taken by various research groups in designing tight binding inhibitors of this enzyme are presented. Although these examples are for HIV-1 protease, they can be applied as a guide for designing inhibitors of other retroviral proteases. This chapter thus provides a chemist's approach in the design and preparation of protease inhibitors.
>
> The approach for designing enzyme inhibitors has involved various methods. When a researcher is confronted with a new proteolytic enzyme, the initial question explored is the sequence and optimal size of the substrate. Once this is known, a medicinal chemist designs possible inhibitors based on the optimal substrate. The usual strategy employed is to replace the scissile bond of the substrate with nonhydrolyzable transition-state analogs that mimic this bond. On identification of a lead compound, amino acid residues in the inhibitor are deleted and/or substituted with isosteres to find the optimal inhibitor. Concurrently, known inhibitors of related proteases are screened for activity against the desired enzyme. Using this approach, many groups have identified renin inhibitors that were active against HIV-1 protease and many of these compounds have been subsequently developed into potent and selective inhibitors.

We point out that it is well established that the test for enablement is whether one skilled in the art would have been able to make and use the claimed invention based on the teachings in the specification coupled with information known in the art, without undue experimentation. United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223, (Fed. Cir. 1988); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The specification "need not teach, and preferably omits, what is well known in the art." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). Since Vacca establishes that protease inhibitors comprising transition-state isosteres, as well as methods of designing and preparing said isosteres, were well known in the art at the time the application was filed, the specification need not disclose more than a few representative examples, to enable those skilled in the art to make and use the claimed invention.

In addition, with respect to the amount of direction provided by the specification, we find that it discloses an assay to test the efficacy of any newly-developed inhibitors comprising a transition-state isostere. See, the specification, pp. 16-18.

Thus, since numerous transition-state isosteres capable of inhibiting aspartic acid proteases were well known in the art, as well as methods of designing new ones, and the specification and Vacca disclose screening assays for testing isosteres for their efficacy as inhibitors, we find that the specification, in combination with knowledge

generally available in the art, would have enabled one skilled in the art to make and use the claimed invention. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94.

Accordingly, Rejection I is reversed.

II. 35 U.S.C. § 112, first paragraph (written description)

The examiner argues that a transition state isostere is a compound wherein two carbon atoms in the tetrahedral conformation mimic the transition state of catalysis. Answer, p. 7. According to the examiner, of all the examples disclosed in the specification, only one compound, UIC-98-056, has two carbons in the tetrahedral conformation. Id. Thus, the examiner contends that the specification fails provide an adequate written description of all the compounds within the scope of the claims. Id.

In response, the appellants argue that the specification discloses an aspartyl protease inhibitor comprising two transition state isosteres as well as other types of transition state isosteres directed to aspartic acid proteases. Brief, p. 14. The appellants further argue that a transition-state isostere is one which replaces the scissile bond of the substrate with a non-hydrolysable transition state analog such that it mimics a substrate peptide. Id. The appellants point out that "the specification discloses a strategy for replacing the scissile bond of the substrate with a non-hydrolysable transition state analog that mimics this bond." Id. Thus, the appellants contend that the specification satisfies the written description requirement of § 112.

In order to satisfy the written description requirement of 35 U.S.C. 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

First, we find that the claims are directed to inhibitors which comprise isosteres which (i) have different orientations; (ii) mimic the transition state of the substrate; and (iii) bind to different subsite binding pockets in the protease.

Second, we agree with the examiner that the specification exemplifies one aspartic acid protease inhibitor having the claimed characteristics; however, attention is directed to the summary of the invention (p. 4, line 25- p. 5, line 4) which states:

> Protease inhibitors, especially viral protease inhibitors such as HIVPr inhibitors, which are effective against drug resistance resulting from the mutations in the protease gene have been developed. These compounds contain two or more isosteres - CH(OH)-CH_2 - which mimic the transition state in the catalytic mechanism of the protease. Design and testing of the inhibitors containing two or more isosters [sic] is demonstrated using a HIVPr inhibitor. Unlike known commercial HIVPr inhibitors, these inhibitors do not contain only one isoster [sic] having a single orientation which binds to the HIVPr active site at only one mode. These HIVPr inhibitors bind to the HIVPr in two or more modes. They not only bind to the protease active site more tightly, but exhibit significantly better activity against HIVPr-resistant mutants and are less prone to [the] development of resistance.

The specification (p. 5, lines 23-26) further discloses that

> The design and testing of these protease inhibitors is exemplified using HIVPr inhibitors. It is understood, however, that this concept is generally applicable to protease inhibitors, especially aspartic acid protease inhibitors.

In our view, these and similar teachings in the specification reasonably convey to those skilled in the art that the appellants were in possession of the claimed invention at the time the application was filed.

Accordingly, Rejection II is reversed.

III. 35 U.S.C. § 102(b)

The examiner argues that the claimed subject matter is anticipated by the teachings of Jadhav I and Jadhav II with respect to aspartic acid protease inhibitors having two or more isosteres which mimic the transition state of aspartic acid protease. Answer, p. 8. The examiner further argues that the patents disclose that the inhibitors described therein inhibit HIV protease. Id. The examiner points to several compounds disclosed in the patents, for support. Id., pp. 8-9. We agree with respect to the teachings of Jadhav I.

It is well established that anticipation requires that each and every limitation set forth in a claim be present, either expressly or inherently, in a single prior art reference. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999); Celeritas Techs. Ltd v. Rockwell Int'l Corp., 150 F.3d 1354, 1360, 47 USPQ2d 1516, 1522 (Fed.

Cir. 1998); Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 730 F.2d 1452, 1458, 221 USPQ 481, 485 (Fed. Cir. 1984).

Contrary to the appellants' argument, we find that Jadhav I discloses numerous compounds which comprise "two or more" transition-state isosteres which are said to inhibit viral replication. See, e.g., Jadhav I, col. 2, lines 16-25 and col. 47, examples 52, 56 and 57. For example, we direct attention to the aforementioned examples in col. 47 which disclose inhibitors comprising a dihydroxyethylene moiety and a "W" moiety. Jadhav I further discloses that "W" can be a CH_2CHOH (example 52), a $CHOHCH_2$ (example 56) and CHOHOH (example 57). Since R^1 in the referenced examples is a benzyl moiety, it reasonably appears that Jadhav I discloses two or more transition-state isosteres which have different orientations. In addition, since Jadhav I discloses that the compounds disclosed therein inhibit HIV replication, it further appears that said compounds mimic the transition state of the HIV aspartic acid protease and bind to different subsite binding pockets in said protease. Thus, on this record, we are unable to find any characteristics which distinguish the prior art aspartic acid protease inhibitors from those which are recited in claims 1, 2, 4, 6-8, 10 and 12. Since the USPTO is not in a position to test prior art compounds and compare them with the appellants' invention, the burden now shifts to the appellants to establish that the claimed compounds differ from those taught by Jadhav I; i.e, that the claimed

compounds are novel under 35 U.S.C. § 102(b). As stated in In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977), quoting In re Swinehart, 439 F.2d 210, 212-13, 169 USPQ 226, 229 (1971):

> [I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on [58 CCPA at 1031, 439 F.2d at 212-213, 169 USPQ at 229.] This burden was involved in In re Ludtke, 58 CCPA 1159, 441 F.2d 660, 169 USPQ 563 (1971), and is applicable to product and process claims reasonably considered as possessing the allegedly inherent characteristics.

Accordingly, absent evidence to the contrary, we find that the teachings of Jadhav I anticipate the claimed invention.[1]

As to the appellants' contention that "the different orientations are critical for stability, binding affinity, and efficacy with regard to protease inhibition and protease resistance mechanisms,"we point out that the claims do not require any specific level of

[1] In affirming the rejection, it was only necessary for us to address the compounds in column 47 of Jadhav 1 which the examiner indicates anticipate the claimed invention. However, in the event of further prosecution of the application, the appellants must demonstrate that the claimed invention is not anticipated by any of the compounds listed on page 9 of the examiner's Answer.

stability, etc. Thus, we find that this argument does not address a limitation present in the claims.

Accordingly, Rejection III is affirmed.

In view of the foregoing, the decision of the examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

JOAN ELLIS
Administrative Patent Judge

DONALD E. ADAMS
Administrative Patent Judge

ERIC GRIMES
Administrative Patent Judge

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